Aus der
Universitäts-Hautklinkik Tübingen

Prospective, randomized and controlled trial to investigate the effect of two application methods for local anesthesia on the patients

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zu Tübingen

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Chen, Mingyi
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aus Chengdu, China

Dekan:	Professor Dr. B. Pichler
1. Berichterstatter:	Professor Dr. H. Breuninger
2. Berichterstatter:	Professor Dr. H.-M. Häfner
3. Berichterstatter:	Professor Dr.Peter Martus
4. Berichterstatter:	Professorin Dr. M. A. Rieger

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Index

List of Figures

List of Tables

List of Charts

1. Introduction

Local anesthesia is the most widely applied anesthetic method in dermatological surgery. Compared with general anesthesia, it's safer and more practical with much less demand for time and labor investment.

Among various kinds of local anesthesia, **local infiltration anesthesia (LIA)** dominates in routine dermatological surgery. By LIA, the anesthetic solution should be directly injected into dermis, subcutaneous tissue or deeper, in order to obtain analgesia effect during and a certain period after surgery. However, the process of LIA, itself may be painful due to the initial needling or the consequent injection, which causes the tension and affects baroreceptor in sensory nerve terminals. On the other hand, some commercial anesthetic solutions cause burning because the solution has a low pH degree, or are not isoionic. Therefore, how to reduce the pain during the process of LIA, to improve the analgesia effect, and to bring the patients better operative experience, remains a persistent topic which attracts the concerns of all relative surgeons and anesthetists.

In routine LIA, most operators inject the anesthetic solution into tissues by hand **(hand-actuated anesthesia，HA),** which has been applied for more than a century. HA has several advantages:

1) It's very flexible. According to the operative location, size, the skin tension and the patient's tolerance of pain, the operator could use different injection methods (single spot, three or multiple spots), the injection speed, and the injection layer (into dermis or subcutaneous tissue). So the pain during the injection process could be limited to minimal extent.
2) Back-suction could be used to confirm whether the needle was injected into vessels accidently, especially in artery. It's well known, the serious toxic reaction could happen when the anesthetic solution was injected into vascular vessels, such as CNS excitation, cardiovascular inhibition, hemangiectasis[1;2].

By HA, the operator could use back-suction method to confirm the location of the needle, whenever the location is altered, in order to avoid the potential complication.

3) The requirement for facility is very limited. The only things needed are a syringe, needle and the doctor's hands.

However, HA has its own disadvantage respectively:

1) It costs plenty of time. During HA, the operator should be always on the patient's side. Especially when the patient has intensive anxiety or lack tolerance of pain, the doctor needs to spend a lot of time for the preparation before operation.
2) Some patients, especially very young ones, may complain, when the doctor stands by for too long, which may bring them extra anxiety and may result in unexpected cardiovascular problems.

On the other hand, some studies showed some methods, e.g. the ice compress, vibration, solution warming, and buffering, etc., can attribute to reduce the pain during the process of HA[3;4;5;6]. Some of these methods indeed relieved the pain during process of HA, however, extra preparation or operation during HA were required.

In dermatological department of Tuebingen University, the **subcutaneous infusion local Anesthesia (SIA)** method, which was introduced by H. Breuninger, has been applied in all sort of dermatological surgery for decades[7]. Aiming at analgesia by SIA, the operator should use the infusion pump to inject the anesthetic solution into subcutaneous tissue or even deeper, like a paravenous infusion which spreads by itself within the tissue. The injection flow of the pump was very low, between 30 and 1500 ml/h (0.01 to 0.4 ml/second).Through SIA, multiple patients could be offered anesthesia by one operator at the same moment, with the convenience of sparing abundant precious time. Besides,

when the pressure rises to a certain level, the infusion pump would stop automatically, so that the excessive pumping could be prevented. This process keeps SIA as an optimal anesthetic option with high security. Furthermore, according to the patient's condition, the pumping speed and volume of SIA could be adjusted, which results in individual pain-relieving process. The patients could quietly rest during the anesthetic period, instead of asking the operator with anxiety from time to time.

Among sorts of local anesthesia, the available medicines include cocaine, procaine, lidocaine, ropivacaine, marcaine, carbocaine, prilocaine, etc. with different concentrations, with or without epinephrine[8;9]. However, these drugs have their own benefits and disadvantages. For example, as the first clinical-applied local anesthetic, which was isolated from main alkaloid of the coca plant, cocaine had the depressant action of on both circulation and respiration[10]. Its intense vasoconstriction mediated by a-adrenergic stimulation can lead to coronary artery spasm [11] and even to myocardial infarct. Thus, severe cocaine toxicity ranging from convulsions to death was reported in serial cases[12]. Compared with cocaine, lidocaine which was introduced in 1949 was much less toxic and it is the most used local anesthetic drug until today, with mild side effects. Neurologic symptoms such as convulsions, loss of consciousness or agitation and cardiovascular symptoms including bradycardia, hypotension and cardiac arrhythmias can occur as a result of toxic plasma levels are the most common systemic side effects from local anesthesia, but they are very rare. Bupivacaine, which was introduced in 1965, had rapidly gained popularity because of its long duration of action and less toxicity[13]. However, the mild to severe central nervous system (CNS) and cardiovascular (CV) toxicity were still reported in 1960's[14]. Bupivacaine is a racemic mixture while ropivacaine is pure (S) enantiomer. With infiltration anaesthesia ropivacaine has a longer duration than bupivacaine, probably because bupivacaine has more vasodilator activity. With the same reason, ropivacaine lasted longer before absorbed into the systemic circulation than bupivacaine, especially with supplementary

of epinephrine[8].

Furthermore, the introduction of tumescent anesthesia is a milestone, which leads to the possibility of large-area operation under local anesthesia. The routine formula of tumescent anesthesia could be the one widely used in liposuction: lidocaine（0.05% or 0.1%), epinephrine (0.65-0.75 mg/L), sodium bicarbonate 10 mg/L, and triamcinolone 10 mg/L as an additional choice[15]. Alternatively, the formula in digital area for tumescent anesthesia without tourniquet could consist of 0.2% lidocaine and 1:1.000.000 epinephrine[16]. The subcutaneous swelling anesthesia provides not only the analgesia of wide extension, with the benefit of epinephrine it also provides the reduced bleeding during the operation, the extended analgesia time, and tolerance of high volume of anesthesia solutions. In the dermatological department of Tuebingen University, a special mixture of different local anesthetic agents (Lidocaine and Ropivacine) highly diluted with Ionosteril®-solution is used. This solution has proved first not to cause burning during injection, second having a very good effectiveness and third having a very long duration. Three different concentrations (0.21%, 0.11% and 0.05%) of SIA have been administrated in routine dermatological surgery for decades, with subcutaneous infusion volumes of up to 1.5 liters.

Table 1. The formula of the anesthetic

	Volume in ml	Lidocaine Xylocain®	Ropivacaine Naropin®	Suprarenin- 1 :1000.000
0,21 % 3 ml / Kg (Adult. 225 ml)	Bag 500 ml Ionosteril®	50 ml 2 %	20 ml 1 %	0,5 ml in 500 ml
0,11 % 6 ml / Kg (Adult 450 ml)	Bag 500 ml Ionosteril®	20 ml 2 %	20 ml 1 %	0,5 ml in 500 ml
0,05 % 12 ml / Kg (Adult. 900ml)	Bag 500 ml Ionosteril®	10 ml 2 %	10 ml 1 %	0,5 ml in 500 ml

The lower the concentration is, the longer time it would takes for the on-set time of the

analgesia, which may maximally rise up to 30minutes if the lowest concentration is used[17]. Among most kinds of surgery, especially the large-area operation, e.g. large-size defect repair, pathological scar, sentinel node biopsy, lymph node dissection and varicose vein surgery.

Aim of the study

Up to 1985 in the department of dermatology of the Universitiy in Tuebingen local anesthesia was performed by hand with the commercial available solution of lidocaine in a fix combination with epinephrine of 1:100.000 in a concentration of 1% (Xylocaine with epinephrine ®). This solution has a low pH degree, and it's not isoionic. Therfore, patients still had pain by injection and the fear by multiple injections at several locations during following days, if reoperations were necessary. SIA with this new formula was introduced in 1985. Since then, the users recognized an amazing reduction of pain. The users referred this reduction to the comfortable slow infiltration by the Infusomat (by SIA with a flow of 0.01 to 0.4 ml/sec) rather than the new mixture, but never proved this by a study up to now.

This study aims at comparing the suggested superiority of SIA to HA concerning the pain during infiltration by a randomized design. But in contrast to the past, the same mixture of local anesthetics was used. The speed of injection was restricted to 0.5 ml/sec. Pain evaluation during the anesthetic process, during and after smaller operations with volumes up to 160ml was done. Then the conclusion whether SIA may prevail over HA could be drawn.

2. Patients and methods

This study was a prospective, randomized, controlled trial. It was held from January to August 2015, in the dermatological department of Tuebingen University, which locates in **Liebermeisterstraße 25, 72076 Tübingen.**

The study was approved by the ethical commission of medical faculty of Tuebingen University. The project-number is 625/2014B01.

The title of the study is “Prospective, randomized and controlled trial to investigate the effect of two application methods for local anesthesia on the patients”

The questionnaire had been established and improved by Prof. Helmut Breuninger, and Dr. Saskia Schnabl. A calculation of the needed cases was not performed, because the mentioned persons expected a really good visible difference between both groups, in favor of the SIA-method. This was a result of their historic experience after the introduction of SIA.

The difference of pain between the use HA with a commercially available solution in combination with suprarenin were used (Xylocaine+epinephrine 1:100.00®) and SIA when it was introduced was amazing. Therefore 100 estimated patients in each arm of the study was a high number to detect a large difference.

Randomization was performed by the Department of Clinical Epidemiology and Applied Biometry of Tuebingen University . The information, concerning the method which will be applied to each patient, was carried out by Prof. Häfner.

2.1 Collection of patients

From 26 Jan. to 21 Aug. 2015, 200 patients who received the primary tumor excision and waited for the consequent defect closing, were involved to this study. All the patients were completely informed before they were involved.

Universitätsklinikum Tübingen
Universitäts-Hautklinik
Ärztlicher Direktor
Prof. Dr. med. M. Röcken
Liebermeisterstr. 25
D- 72076 Tübingen
Tel: Pforte (0 70 71) 29-84 55 5

PATIENTENINFORMATION

Vergleichende Untersuchung zur Schmerzempfindung bei unterschiedlicher Durchführung einer örtlichen Betäubung

Studienzentrum: Universitäts-Hautklinik, Liebermeisterstr. 25, 72076 Tübingen
Studienleiter: *Prof. Dr. med. Helmut Breuninger*
Prüfärzte: Dr. med. Saskia Schnabl, Dr. med. Claudia Schulz, Dr. med. Markus Krug, PD Dr. med. Hans-Martin Häfner.

Sehr geehrte Patientin, sehr geehrter Patient,
diese Information soll Sie über die Untersuchung zum Schmerzempfinden bei unterschiedlichen Arten der örtlichen Betäubung aufklären.

Grundlagen:
An der Universitäts-Hautklinik werden über 98% aller Operationen in örtlicher Betäubung durchgeführt. Dabei wenden wir die übliche Betäubung durch Spritzen in die Haut an oder eine Betäubung mittels einer Infusion in die Haut. Bei beiden wird das gleiche Anästhetikum verwendet.

Ziel der Studie:
Wir wollen vor allem wissen, wie Sie die Lokalanästhesie und die nachfolgende Operation empfinden.

Studienablauf und Ihre Pflichten:
Sie werden durch Zufall eingeteilt für eine Lokalanästhesie mit der Spritze durch den Arzt oder durch eine Infusion. In beiden Fällen sind sowohl die Nadel als auch das Anästhetikum gleich.

Vorteile einer Studienteilnahme:
Der potenzielle Nutzen für Sie als Patient liegt darin, dass Sie immer vom gleichen in der Lokalanästhesie geübten Arzt betäubt werden.

Risiken:
Es sind die üblichen Risiken der Lokalanästhesie. Es gibt kein erhöhtes Risiko, da es sich um alltäglich angewandte Methoden handelt.

Geheimhaltung:
Alle im Rahmen dieser Studie erhobenen Daten werden von Ihrem Arzt absolut vertraulich behandelt. Die zur statistischen Auswertung dieser Studie notwendigen

Fig.1(a). The informed consent papers to patients (page 1)

2

Daten werden nur anonymisiert bearbeitet und gespeichert. Einsicht in die Krankenakten erhält nur Ihr behandelnder Studienarzt und der Studienleiter. Einsicht in die pseudonymisierten Studienunterlagen (nur eine Kennziffer ohne Namen) erhält ebenfalls der Studienkoordinator. Dadurch wird eine dem Prüfplan gemäße Durchführung der Studie sowie die korrekte Erhebung der Daten sichergestellt. Alle Studienmitarbeiter sind zur absoluten Vertraulichkeit verpflichtet. Falls eine Einsicht der Gesundheitsbehörden oder Bundesoberbehörden auf Grund der erhobenen Daten notwendig werden sollte, werden die Daten komplett anonymisiert.

Sollten Sie Fragen zu dieser Studie haben, können Sie sich jederzeit an Ihren Prüfarzt wenden.

Versicherungsschutz:

Sie sind über die übliche Haftpflichtversicherung des Klinikums versichert.

Information zum Datenschutz:

Ihre im Rahmen der wissenschaftlichen Untersuchung erhobenen Daten werden vertraulich behandelt und ausschließlich in verschlüsselter Form weitergegeben. Die Aufzeichnung der im Rahmen dieser wissenschaftlichen Untersuchung erhobenen Daten erfolgt zunächst in den Originalunterlagen Ihrer Krankenakte, in die Ihr Arzt auch bisher alle Befunde eingetragen hat. Die für die wissenschaftliche Untersuchung wichtigen Daten werden in verschlüsselter (pseudonymisiert, ohne Namensnennung) Form in einen gesonderten Dokumentationsbogen eingetragen.

Die Zuordnung der verschlüsselten Daten zu Ihrer Person ist nur anhand einer Patientenliste möglich, die in einem verschlossenen Schrank, getrennt von den Studienunterlagen, aufbewahrt wird und nur dem Stu¬dien¬leiter und dem Ärztlichen Direktor der Abteilung zugänglich ist. Die Daten werden für die Dauer von 10 – 20 Jahren im Archiv aufbewahrt.

Einwilligungserklärung

Ich erkläre mich mit der Verwendung der im Rahmen dieser Untersuchung erhobenen Daten in der oben beschriebenen Weise einverstanden. Ich kann jeder Zeit meine Daten beim Studienleiter einsehen. Bei meinem Rücktritt aus der Studie werden die bis dahin erhobenen Daten nicht vernichtet.

Tübingen, den	Unterschrift	Name des Patienten/der Patientin in Blockschrift

Fig.1(b). The informed consent papers to patients (page 2)

2.1.1 The Estimation of Sample Size

The sample size of each group was settled to be 100. The reason was given below:

1) On the expectation of SIA better than HA, we chose the Sample-size-estimation formula as below, which is superiority test about the mean-value comparison between two samples.

$$N = \left[\frac{(Z_\alpha + Z_\beta)\sigma}{\delta - \Delta}\right]^2 \left(\frac{1}{Q_1} + \frac{1}{Q_2}\right)$$

α=0.05，β=0.1，thus "u value of standard normal distribution for one side test" was chosen, Z_α=1.645，Z_β=1.282. According to the preliminary experiment, the multiple time-point pain scores σ=1.8, and δ=1.0(Minimum unite of VAS scores)，Δ=0.2. Because the sample size in two groups were comparable, so $Q_1 = Q_2 = 0.5$,thus sample size N=174. Considering the lost follow-up and incooperative cases, a certain expansion is necessary, thus the primary estimation of the sample size in our study is 200 cases, while 100 in each contrastive group.

2）There're several high-quality literatures investigated on similar topic (pain management), in which the sample size were similar or even smaller than 200 cases[5,17,40]. (Li et al. (2017), Schnabl et al. (2012) and Schnabl et al. (2013))

2.1.2 The Inclusion Criteria

a) The patients who were hospitalized after the diagnosis of a primary cutaneous tumor (e.g. basal cell carcinoma, squamous cell carcinoma and malignant melanoma), and the consequent defect closing would be followed.
b) Patients with single-location skin tumor
c) The diameters of defects≤50mm(since the over-size difference

between two groups may brought bias)

d) Patients with normal pain feeling and were able to communicate with the investigator fluently.

2.1.3 The Exclusion Criteria

a) Patients without self-decision ability.

b) Patients without normal pain feeling or unable to communicate with the investigator.

c) Patients with mental diseases.

d) Patients under age of 18.

e) Patients with severe cardiovascular and cerebrovascular diseases.

f) Patients who were unable to accept operation.

g) Patients with multiple-location tumors.

h) The diameters of defects>50mm

According to the inclusion and exclusion criteria, 200 patients who matched the criteria were involved into this study. There were no statistic significant differences between two groups in gender, age, and defect sizes ($p>0.05$).

Table 2. The basic information of all patients

Characteristics	**HA(n=100)**	**SIA(n=100)**	**Significant value(P)**
Gender, n(%)			
Male	65(32.5%)	59(29.5%)	0.382
Female	35(17.5%)	41(20.5%)	
Age, y, median(range)	78（46-94）	75.5（34-89）	0.396
Defect size, mm^2, median(range)	492(15-2080)	326.5(16-1550)	0.541
Tumor locations, n(%)			
Scalp	9(4.5%)	12(6%)	0.081
Face	87(43.5%)	81(40.5%)	0.236
Trunk	1(0.5%)	5(2.5%)	Not comparable
Upper extremities	3(1.5%)	0	Not comparable
Lower extremities	0	2(1%)	Not comparable

2.2 The methods of randomization The computer-generated random numbers, which were obtained from Department of Clinical Epidemiology and Applied Biometry of Tuebingen University, were applied to this study, described above. The randomly generated numbers were used to code the patients instead of the anesthetic methods, which aimed at avoiding the potential bias. All 200 patients were randomized. The purpose of dividing 100 patients into each group had been guaranteed.

2.3 Methods and data collection

2.3.1 The preparation for anesthesia

All the patients were given anesthesia in the preparation rooms before entering the operation rooms. Before the anesthesia, they were fully informed about the purpose, principle, benefit of this study, as well as their rights and obligations during the study. All patients' informed consent were acquired. The patients with extraordinary nervousness were given midazolam (8 patients in HA group, while 11 patients in SIA group, no statistical significant differences), the consent of all the patients before the admission of midazolam was acquired. Both two groups were given the anesthetic with same formula (Table 2.), which have been applied in the dermatological department of Tuebingen University for decades[18]. However, the methods of inducing the anesthetic were totally different.

2.3.2 The procedure of anesthesia before operation

a) Group HA. The anesthetics were injected manually into dermis or subcutaneous tissues, through 5ml syringe with 30G needle. The minimal speed of injection should not be lower than 0.5ml/s (1800ml/h).
The drawing- back test was always done before the injection, to make sure the needle wasn't in vessels. The injection stopped when the skin turned pale and swollen, which was the sign of adequate volume for qualified anesthesia. Multiple-point injection was possible for patients with large defect. When the skin 30mm around the injection point turned pale and swollen, and the operator felt enough resistance from the syringe, the shift of the injection and another injection was necessary. The dose of anesthetic was recorded.

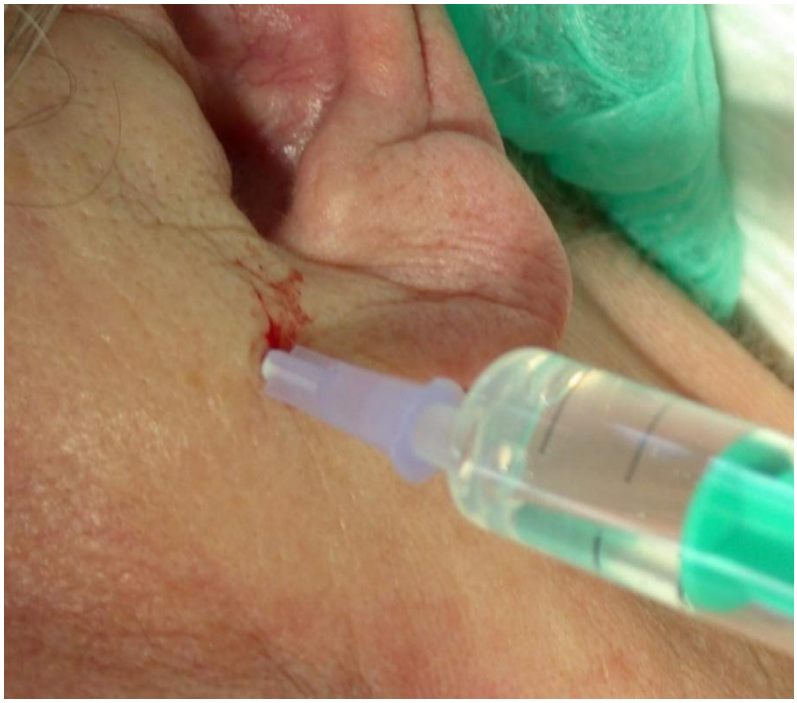

Fig.2.The procedure of HA

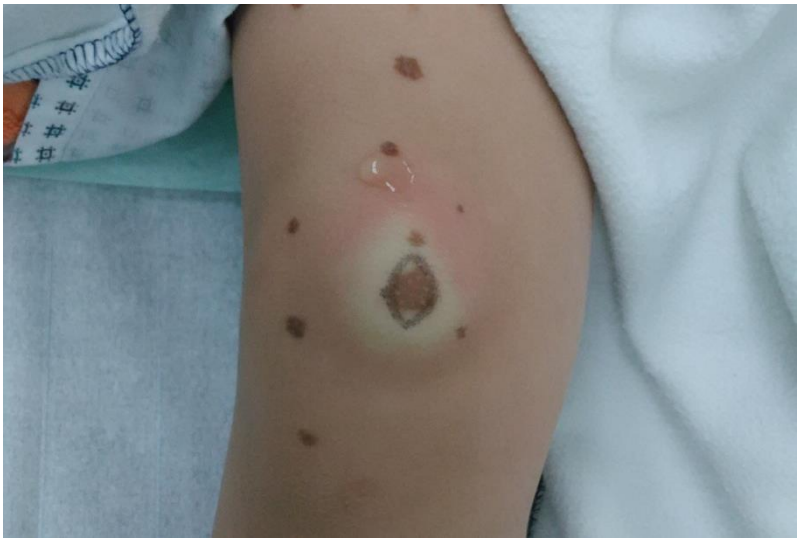

Fig.3 The clinical appearance when enough volume of anesthetics was given: the skin turned pale and swollen.

b) Group SIA. The infusion pumps was connected with 30G needles by infusion tubes. The speed of infusion was adjusted from 30-400ml/h. The estimated volume of anesthetic was 5ml per 100mm^2 of defect size. First of all, the monitor for supervising the vital signs of the patient should be

immediately and correctly installed before SIA. Since During SIA, the operator lacked the opportunity to make drawing- back test, which used to confirm the needle was not in the vessels, was not possible. However, due to the adrenaline in the formula, the increased heart race would trigger the alarm of the monitor if the needle was accidently inserted into vessel. Then the operator expelled the rest air in the tube, and checked again whether the infusion pump was in smooth function. Then the needle of 30G was stabbed into subcutaneous tissues, which was followed by the activation of infusion pump. If the needle wrongly stayed at dermis, the high tension would trigger the alarm and immediately stopped the pump. After a few seconds of observation for making sure the pump worked normally, the needle was fixed with adhesive tap onto the skins stably. The hair in the region should be razed in advance. Afterwards, the operator could leave to take care of another patient waiting for the anesthesia, after a few words to comfort the former one. When the estimated finishing time(normally in minutes) of the anesthetic arrived, or the alarm of the infusion pump was triggered(when adequate anesthetic was infused into subcutaneous tissues, the tension would trigger the alarm), the operator would return to check whether enough anesthesia was achieved. Generally, the paleness and edema of the skin, was a reliable sigh of qualified anesthesia. If the defect was too large for one-spot SIA, the shift of the needle and further infusion was possible. (**Fig.4-6**)

The speed of infusion and volume of anesthetic were recorded.

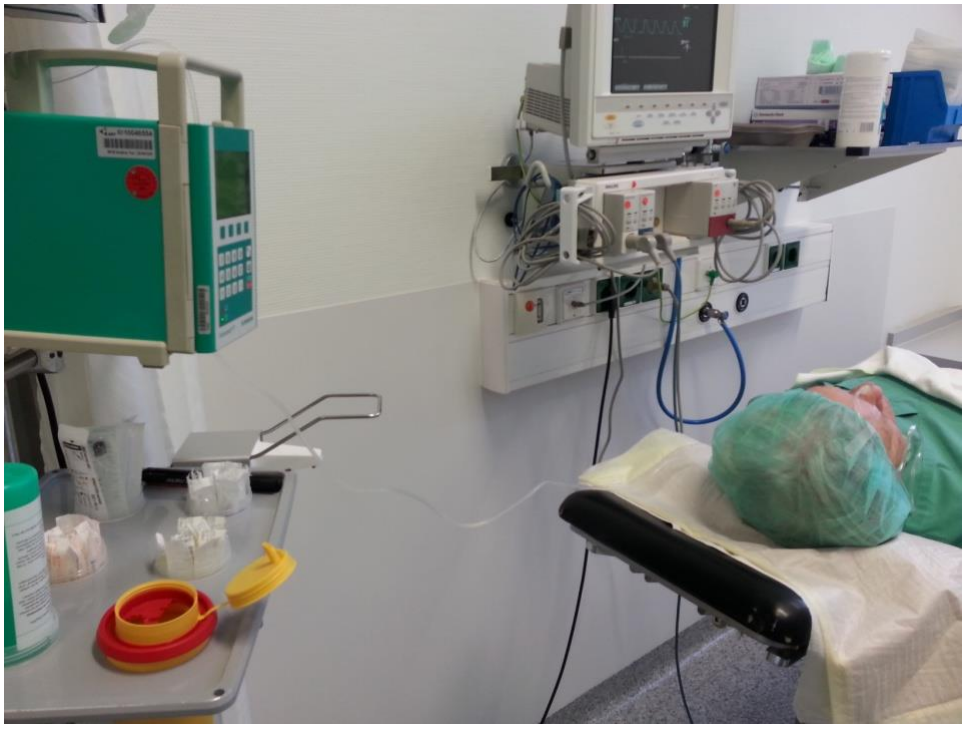

Fig.4 The procedure of SIA

Fig.5 The working status of the Infusomat: the speed of SIA was adjustable, when the pump sounded alarm, the infusion stopped.

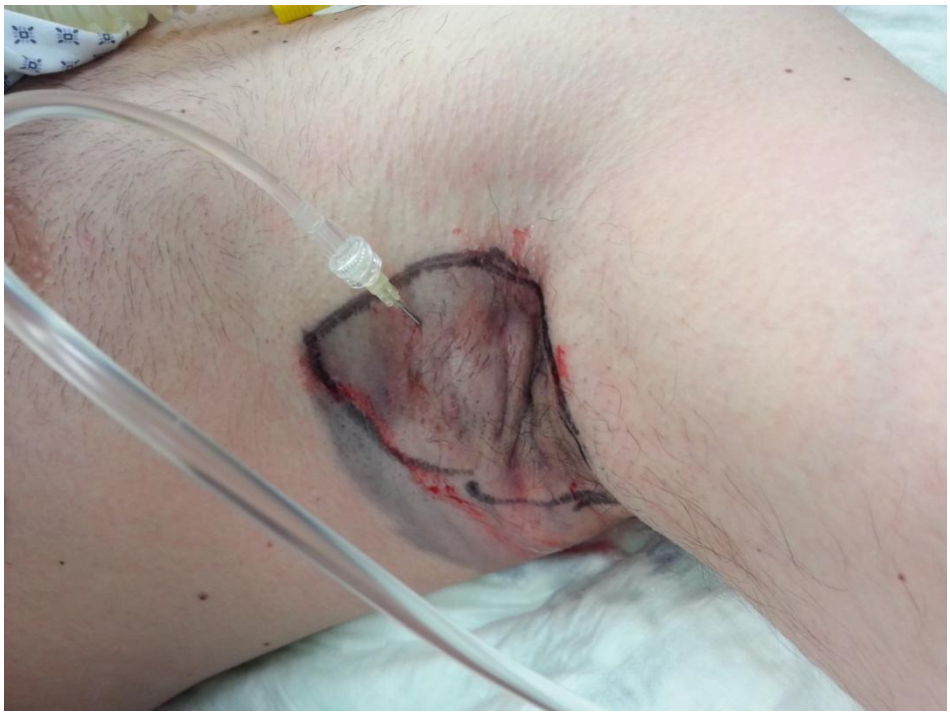

Fig.6 The clinical appearance of the operative region during SIA

2.3.3 Further anesthesia during operation

No matter whether the patient was in group HA or SIA, the further anesthesia was given only if the patient still felt pain during the operation. The anesthetic was given manually by syringe, 0.5ml/s (1800ml/h)(Fig8.). The operation paused until the effect of further anesthesia worked, which was examined by needling. Meanwhile, the dose of the further anesthetic was recorded.

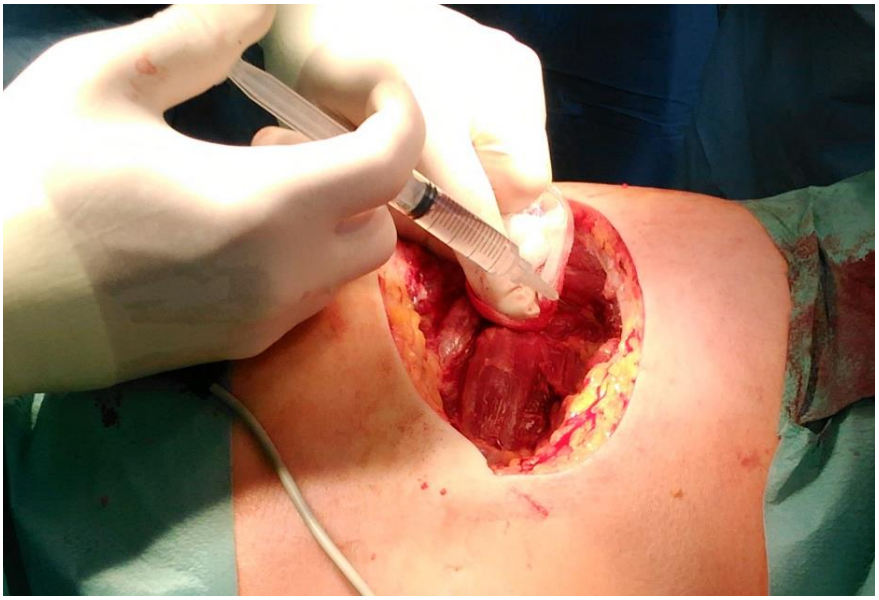

Fig.7 The further anesthesia by HA during operation

2.3.4 Documentation after operation - the questionnaire for patients.

Twenty-four hours after the operations, the assigned investigator (doctoral candidate Mingyi Chen), who also did all local anesthesia procedure in this study, held the well-designed questionnaire to the patients. The questionnaire was designed and improved by Prof. Helmut Breuinger and Dr. Saskia Schnabl. The investigator explained the principle and the methods to fill the papers in details, especially for elderly patients. The main data included pain scores of the initial needling, the consequent needling, during the injection/infusion, and the scores of intraoperative and postoperative pain, as well as the dose of anesthetics, the duration of anesthetic procedure and the severity of anxiety/nervousness before surgery. All the scores were evaluated by Visual Analogue Scale (VAS). The scores were either given by patients when they understood VAS well, or evaluated by the investigator, according to the position of the mark wrote by patients. Besides, whether

the patients needed further anesthesia during operation or not, was also recorded.(Fig8.)

Note: To avoid the operator's bias, all the anesthesia were operated by the same assigned investigator (doctoral candidate Mingyi Chen), who had abundant experience both in HA and SIA. Beside the delivery, the collection of questionnaires was also carried out by Mingyi Chen.

Eberhard-Karls-Universität
UKT
Universitätsklinikum Tübingen

Universitäts-Hautklinik, Liebermeisterstraße 25, 72076 Tübingen

Universitätsklinikum Tübingen
Universitäts-Hautklinik
Ärztlicher Direktor
Prof. Dr. med. M. Röcken
Operative Dermatologie
Ltd. Oberarzt PD Dr. med. H-M Häfner
Arzt für Dermatologie und Phlebologie

☎ Tübingen 07071/
29-83751 Pforte/Vermittlung

29-84577 OA Arbeitszimmer
29-84590 Sekretariat, Frau Merkle
29-4588 Telefax Sekretariat
e-mail: elisabeth.merkle@imed.uni-tuebingen.de

Fragebogen zur Bewertung der örtlichen Betäubung

Sie hatten sich für eine vergleichende Untersuchung bereit erklärt, wofür wir ihnen sehr danken.
Durch ihre Mitarbeit werden zukünftig Patienten einen Nutzen haben.
Wir bitten Sie nun folgende Fragen immer auf den unten aufgeführten Balken mit einem Kreuz wie gezeigt zu beantworten ◆—X—◆ auf Balken ankreuzen

Bitte geben Sie eine Nummer von 0(gut) bis 10(schlecht) aus.

Die **Vorbereitung** auf die OP in örtlicher Betäubung

war gut ◆——◆ schlecht

Vor der Betäubung war ich: nicht angespannt ◆——◆ sehr stark angespannt

Ich bin schmerzempfindlich wenig ◆——◆ sehr stark

Der **Einstich** war: wenig schmerzhaft ◆——◆ sehr schmerzhaft

Bei mehreren Einstichen:

Einige Einstiche waren wenig schmerzhaft ◆——◆ sehr schmerzhaft

Alle Einstiche waren: wenig schmerzhaft ◆——◆ sehr schmerzhaft

Nach den Einstichen:

Das **weitere Einspritzen** war: wenig ◆——◆ sehr schmerzhaft

Die Dauer der Einspitzung war: wie erwartet ◆——◆ unangenehm lang

Die Operation war: nicht schmerzhaft ◆——◆ sehr schmerzhaft

Während der Operation musste nachgespritzt werden: ja O .....nein O (bitte ankreuzen)

Nach der Operation hatte ich: wenig ◆——◆ starke Schmerzen

Eigene Anmerkungen/Kritik zum Ablauf, Operateur, Anästhesist :

Wir sind Ihnen vor allem **auch für Kritik sehr dankbar**, da Sie uns helfen kann, die Patietenversorgung zu verbessern! **Bitte hier Kritik:**

分栏符

Fig.8(a) The questionnaire for patients(page 1)

Patientendaten:

Patientenaufkleber

Name:

Alter:

Geschlecht:

Defektgröße:

Lokalisation:

Folgeeingriff: ja / nein

Defektverschluss: ja / nein
Größe (LängexBreite)

Perioperative Sedativa: wenn ja welches und Dosierung

Postoperative Schmerzrmedikation

Nebenerkranungen:
Diabetes ja / nein, Bluthochdruck ja / nein

Weitere schwere Nebenerkrankungen führen zum Ausschluss.

Datenschutzerklärung

Ich erkläre mich damit einverstanden, dass im Rahmen dieser Befragung erhobene Daten in pseudonymisierter (verschlüsselter) Form auf elektronischen Datenträgern **nur** bei Frau Dr. Schnabl, ärztlicher Mitarbeiter der Universitäts Hautklinik, und den Doktoranten Mingyi Chen, *Liebermeisterstr. 25, 72076 Tübingen* aufgezeichnet werden. Soweit erforderlich, dürfen die erhobenen Daten pseudonymisiert weitergegeben werden: an das Institut für medizinische Biometrie oder eine von diesem beauftragte Stelle zum Zwecke der wissenschaftlichen Auswertung.
Nach der verschlüsselten Auswertung werden alle personenbezogenen Daten gelöscht.

Ort/Datum Name

Fig.8(b) The questionnaire for patients(page 2)

2.4 Statistic analysis

All the data were analyzed by SPSS 19.0(SPSS Inc.). The measurement data were described as $\bar{X} \pm s$, the statistic methods were used as below:

- Mann-Whitney U Test
- Spearman Rank Correlation
- Goodman and Kruskal's Gamma

$P \geqslant 0.05$, no statistical significant differences were considered.

$P < 0.05$, statistical significant differences were considered.

3. Results

By recording the information of all 200 patients, including the pain scores (by VAS) of the initial needling, the consequent needling, during the injection/infusion, and the scores of intraoperative and postoperative pain, as well as the severity of anxiety and the duration of anesthetic procedure, the comparison of SIA and HA groups was performed. Since the consequent needling didn't happen on every patient, it was not comparable for two groups. Thus only the pain on four time points: the initial needling, during the injection/infusion, during and after the operation. Meanwhile, in each group, 6 factors, which might affect the anesthetic effect, including gender, age, defect size, dose of anesthetics, duration of anesthetic procedure and the level of anxiety, were also investigated. The results demonstrated as below:

3.1 **Statistic description of the pain scores of the four time points**

According to statistical analysis, the pain scores of all four time points met the criteria of positive skew distribution. Thus for comparing the pain scores of HA and SIA groups, nonparametric test-- Mann-Whitney U Test was applied to analyze the results. (**Chart 1**)

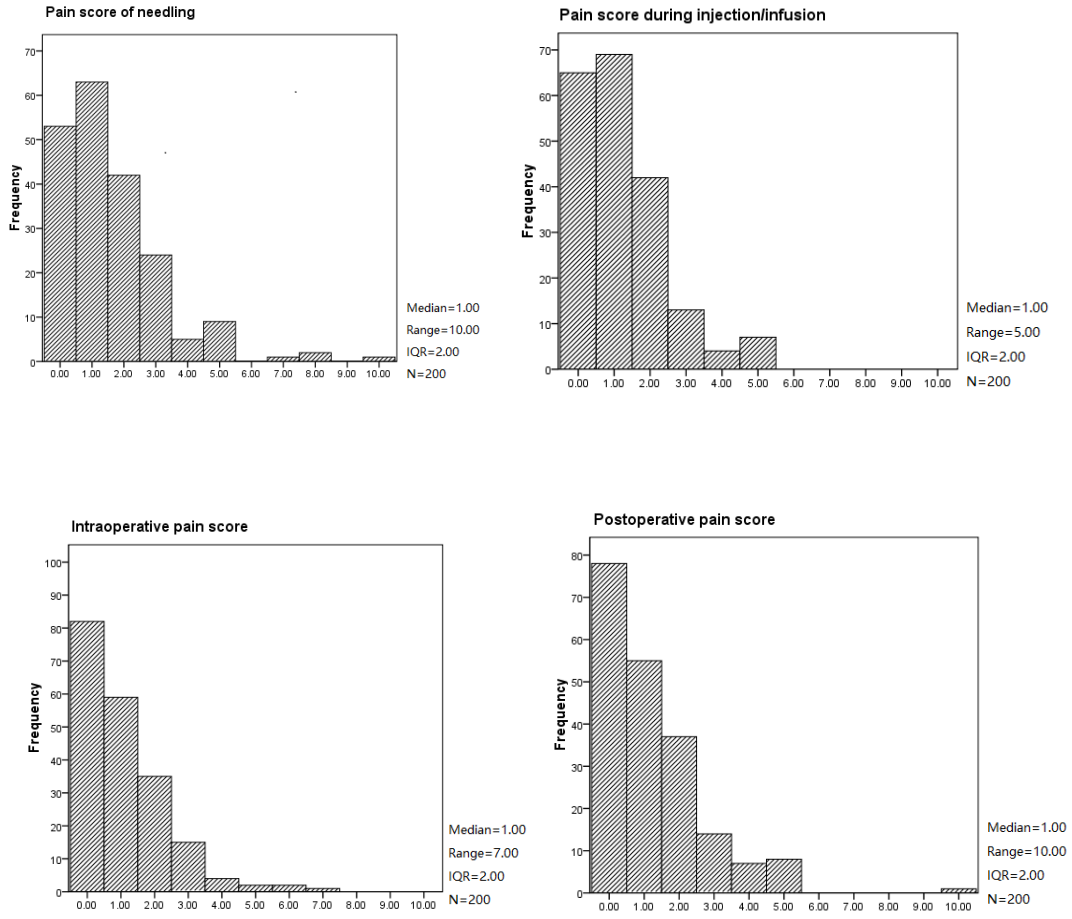

Chart 1. The pain scores of the four time points. T**he pain scores of all four time points were positive skew distribution**

3.2 Comparison of HA and SIA groups about the pain scores of all four time points

Mann-Whitney U Test was applied to evaluate the pain scores of the initial needling, during the injection/infusion, during and after the operation. The results showed **no statistical significant differences** between HA and SIA groups on all four time points.

a) **Pain scores of initial needling.** Compared with HA group, SIA group showed no statistic differences in pain evaluation of needling. Value of Z equaled to -0.6, Value of P equaled to 0.548.

b) **Pain scores during injection/infusion**. Compared with HA group, SIA group showed no statistic differences in pain evaluation during injection/infusion. Value of Z equaled to -0.448, Value of P equaled to 0.654.

c) **Pain scores during operation.** Compared with HA group, SIA group showed no statistic differences in pain evaluation during operation. Value of Z equaled to -1.391, Value of P equaled to 0.164.

d) **Pain scores after operation.** Compared with HA group, SIA group showed no statistic differences in pain evaluation of needling. Value of Z equaled to -0.403, Value of P equaled to 0.687.

The results were demonstrated in Chart 2.

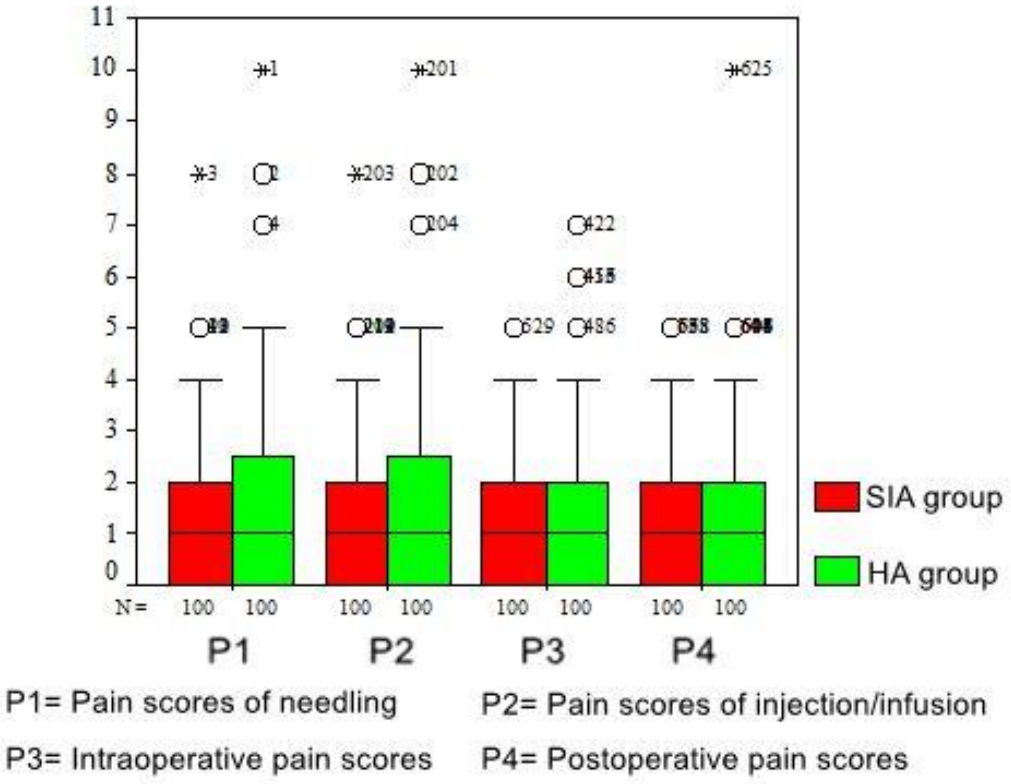

Chart 2. The comparison between HA and SIA groups on the pain scores of all four time points. No statistical significant differences between HA and SIA groups on all four time points.

3.3 The investigation on the six factors which might affect the final anesthetic effects.

3.3.1 Gender

Since the data of gender also met the criterion of nonparametric test, the Mann-Whitney U Test was applied to analyze the results.

HA group

a) About the pain scores of initial needling. Z=-1.616, P=0.106. No statistical significant differences were noticed, which indicated Gender didn't affect the pain scores of initial needling in HA group.

b) About the pain scores of injection/infusion. Z=-2.438,

P=0.015.Statistical significant differences were noticed, which indicated Gender did interfere the pain of injection/infusion in HA group. The female patients demonstrated higher pain scores.

c) About the pain scores during operations. Z=-1.717, P=0.086. No statistical significant differences were noticed, which indicated Gender didn't affect the pain scores during operations in HA group.

d) About the pain scores after operations. Z=-1.128, P=0.259. No statistical significant differences were noticed, which indicated Gender didn't affect the pain scores after operations in HA group.

SIA group

a) About the pain scores of initial needling. Z=-1.133, P=0.257. No statistical significant differences were noticed, which indicated Gender didn't affect the pain scores of initial needling in SIA group.

b) About the pain scores of injection/infusion. Z=-0.260, P=0.795. No statistical significant differences were noticed, which indicated Gender didn't interfere with the pain of injection/infusion in SIA group.

c) About the pain scores during operations. Z=-0.394, P=0.694. No statistical significant differences were noticed, which indicated Gender didn't affect the pain scores during operations in SIA group.

d) About the pain scores after operations. Z=-0.365, P=0.715. No statistical significant differences were noticed, which indicated Gender didn't affect the pain scores after operations in SIA group.

3.3.2 Age

Since Ages were quantitative data, and the pain scores met the criteria of skewed distribution, the analysis of Spearman Rank Correlation was applied.

HA group

a) About the pain scores of initial needling. Correlation coefficients =0.088, P=0.384. No statistical significant differences were noticed, which indicated Age didn't affect the pain scores of initial needling in HA group.

b) About the pain scores of injection/infusion. Correlation coefficients =0.234, P=0.019. Statistical significant differences were noticed, which indicated Age did interfere with the pain scores of injection/infusion in HA group. Age demonstrated positive correlation with pain scores of injection/infusion in HA group (**Chart 3**.).

c) About the pain scores during operations. Correlation coefficients =0.195, P=0.051. No statistical significant differences were noticed, which indicated Age didn't affect the pain scores during operations in HA group.

d) About the pain scores after operations. Correlation coefficients =0.010, P=0.921.No statistical significant differences were noticed, which indicated Age didn't affect the pain scores after operations in HA group.

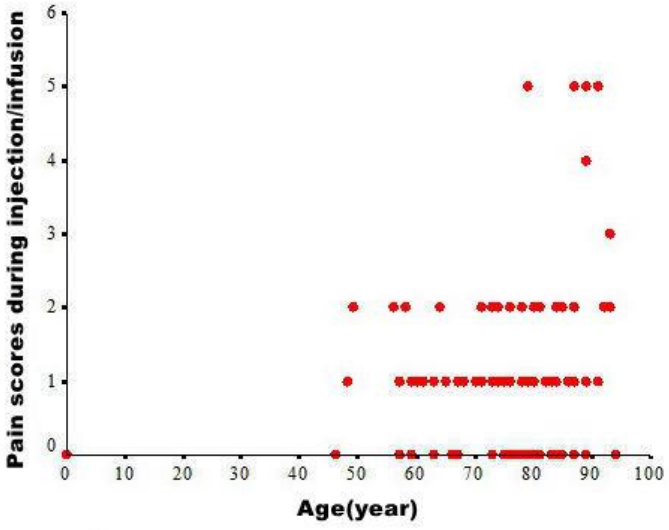

Chart 3. The correlation diagram between Age and Pain Scores of injection/infusion in HA group. Positive correlation was observed (P=0.019).

SIA group

a) About the pain scores of initial needling. Correlation coefficients =0.151, P=0.135. No statistical significant differences were noticed, which indicated Age didn't affect the pain scores of initial needling in SIA group.

b) About the pain scores of injection/infusion. Correlation coefficients =0.146, P=0.148. No statistical significant differences were noticed, which indicated Age didn't affect the pain scores of injection/infusion in SIA group.

c) About the pain scores during operations. Correlation coefficients =0.123, P=0.223. No statistical significant differences were noticed, which indicated Age didn't affect the pain scores during operations in SIA group.

d) About the pain scores after operations. Correlation coefficients =0.029, P=0.773.No statistical significant differences were noticed, which indicated Age didn't affect the pain scores after operations in SIA group.

3.3.3 Size of defects

Since the size of defects was quantitative data, and the pain scores met the criteria of skewed distribution, the analysis of Spearman Rank Correlation was applied.

HA group

a) About the pain scores of initial needling. Correlation coefficients =0.126, P=0.21. No statistical significant differences were noticed, which indicated Size of defects didn't affect the pain scores of initial needling in HA group.

b) About the pain scores of injection/infusion. Correlation coefficients =0.134, P=0.185. No statistical significant differences were noticed, which indicated Size of defects didn't interfere with the pain scores of injection/infusion in HA group.

c) About the pain scores during operations. Correlation coefficients =0.105, P=0.298. No statistical significant differences were noticed, which indicated Size of defects didn't affect the pain scores during operations in HA group.

d) About the pain scores after operations. Correlation coefficients =0.245, P=0.014.Statistical significant differences were noticed, which indicated Size of defects did affect the pain scores after operations in HA group. Size of defects demonstrated positive correlation with pain scores after operations in HA group (**Chart 4.).**

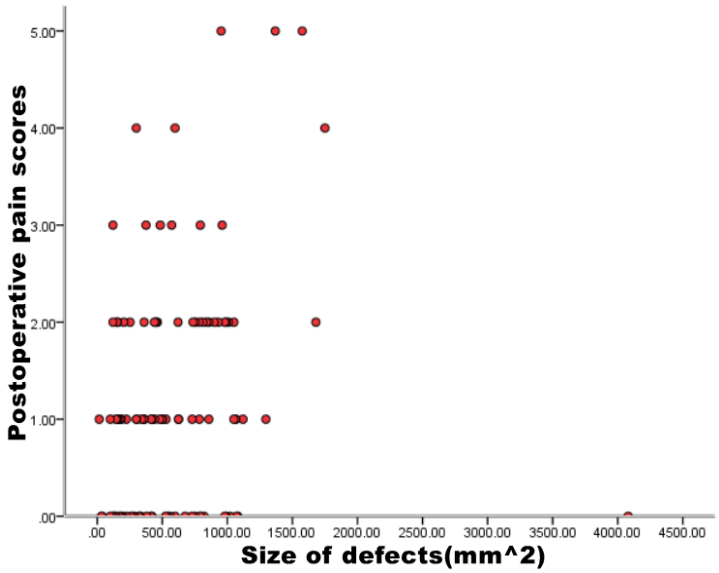

Chart 4. The correlation diagram between Size of defects and postoperative pain scores in HA group. Positive correlation was observed (P=0.014).

SIA group

a) About the pain scores of initial needling. Correlation coefficients =0.066, P=0.512. No statistical significant differences were noticed, which indicated Size of defects didn't affect the pain scores of initial needling in SIA group.

b) About the pain scores of injection/infusion. Correlation coefficients =0.086, P=0.396. No statistical significant differences were noticed, which indicated Size of defects didn't affect the pain scores of injection/infusion in SIA group.

c) About the pain scores during operations. Correlation coefficients =0.141, P=0.161. No statistical significant differences were noticed, which indicated Size of defects didn't affect the pain scores during operations in SIA group.

d) About the pain scores after operations. Correlation coefficients =0.019, P=0.851.No statistical significant differences were noticed, which indicated Size of defects didn't affect the pain scores after operations in SIA group.

3.3.4 Dose of anesthetics

Since Dose of anesthetics was quantitative data, and the pain scores met the criteria of skewed distribution, the analysis of Spearman Rank Correlation was applied.

HA group

a) About the pain scores of initial needling. Correlation coefficients =0.119, P=0.240. No statistical significant differences were noticed, which indicated Dose of anesthetics didn't affect the pain scores of initial needling in HA group.

b) About the pain scores of injection/infusion. Correlation coefficients =0.051, P=0.615. No statistical significant differences were noticed, which indicated Dose of anesthetics didn't interfere with the pain scores of injection/infusion in HA group.

c) About the pain scores during operations. Correlation coefficients =0.032, P=0.753. No statistical significant differences were noticed, which indicated Dose of anesthetics didn't affect the pain scores during operations in HA group.

d) About the pain scores after operations. Correlation coefficients =0.104, P=0.302. No statistical significant differences were noticed, which indicated Dose of anesthetics didn't affect the pain scores after operations in HA group.

SIA group

a) About the pain scores of initial needling. Correlation coefficients =0.116, P=0.252. No statistical significant differences were noticed, which indicated Dose of anesthetics didn't affect the pain scores of initial needling in SIA group.

b) About the pain scores of injection/infusion. Correlation coefficients

=0.004, P=0.968. No statistical significant differences were noticed, which indicated Dose of anesthetics didn't affect the pain scores of injection/infusion in SIA group.

c) About the pain scores during operations. Correlation coefficients =0.130, P=0.199. No statistical significant differences were noticed, which indicated Dose of anesthetics didn't affect the pain scores during operations in SIA group.

d) About the pain scores after operations. Correlation coefficients =0.079, P=0.434.No statistical significant differences were noticed, which indicated Dose of anesthetics didn't affect the pain scores after operations in SIA group.

3.3.5 Time-period of anesthetic procedure

Since time-period of anesthetic procedure were ordered-bivariate data, and the pain scores met the criteria of skewed distribution, the analysis of Goodman and Kruskal's Gamma was applied.

HA group

On all four time points, the relationship of Duration of anesthetic procedure and pain scores demonstrated statistical significant differences in HA group. **(Chart 5)**

a) About the pain scores of initial needling. Gamma=0.659, P<<0.01. Statistical significant differences were noticed, which indicated time-period of anesthetic procedure did affect the pain scores of initial needling in HA group.

b) About the pain scores of injection/infusion. Gamma=0.787, P<<0.01.Statistical significant differences were noticed, which

indicated time-period of anesthetic procedure did interfere the pain scores of injection/infusion in HA group.

c) About the pain scores during operations. Gamma=0.616, P<<0.01.Statistical significant differences were noticed, which indicated time-period of anesthetic procedure did affect the pain scores during operations in HA group.

d) About the pain scores after operations. Gamma=0.559, P<<0.01.Statistical significant differences were noticed, which indicated time-period of anesthetic procedure did affect the pain scores after operations in HA group.

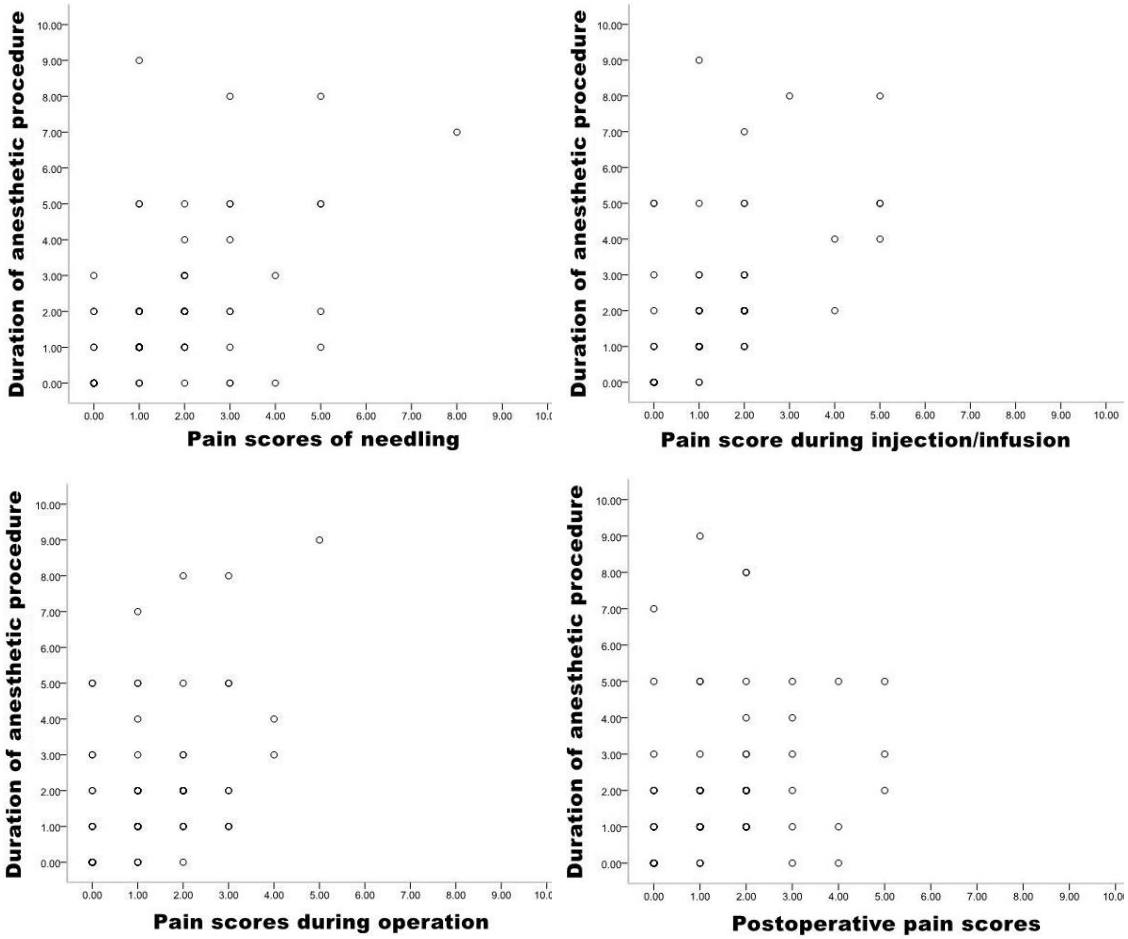

Chart 5. The correlation diagram of time-period of anesthetic procedure procedure and pain scores in HA group. The time-period of anesthetic procedure did affect all four-timing pain scores in HA group (P<0.05)

SIA group

On all four time points, the relationship of Duration of anesthetic procedure and pain scores demonstrated statistical significant differences in SIA group. (**Chart 6**)

a) About the pain scores of initial needling. Gamma=0.541, P<<0.01.Statistical significant differences were noticed, which indicated time-period of anesthetic procedure did affect the pain scores of initial needling in SIA group.

b) About the pain scores of injection/infusion. Gamma=0.730, P<<0.01.Statistical significant differences were noticed, which indicated time-period of anesthetic procedure did affect the pain scores of injection/infusion in SIA group.

c) About the pain scores during operations. Gamma=0.632, P<<0.01.Statistical significant differences were noticed, which indicated time-period of anesthetic procedure did affect the pain scores during operations in SIA group.

d) About the pain scores after operations. Gamma=0.536, P<<0.01.Statistical significant differences were noticed, which indicated time-period of anesthetic procedure did affect the pain scores after operations in SIA group.

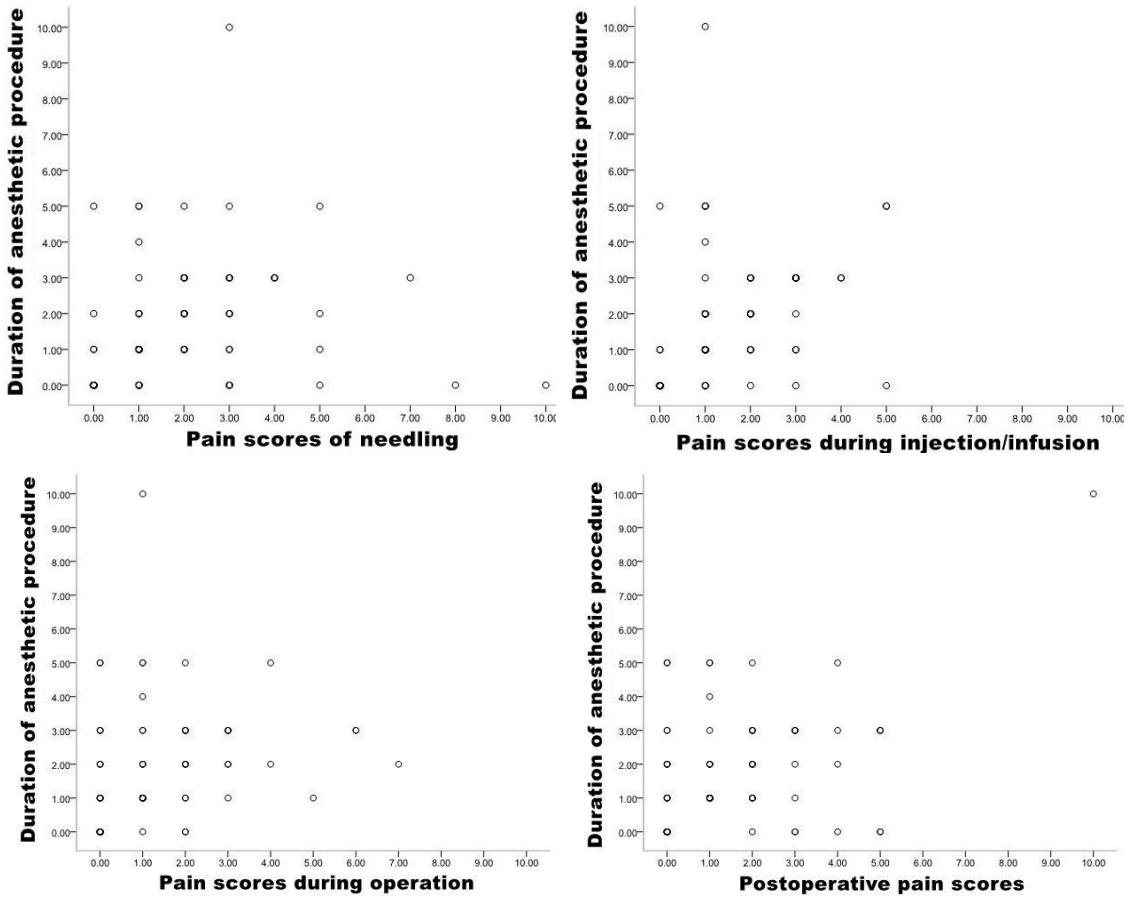

Chart 6. The correlation diagram of time-period of anesthetic procedure and pain scores in SIA group. The time-period of anesthetic procedure did affect all four-timing pain scores in SIA group (P<0.05)

3.3.6 The severity of anxiety/nervousness before surgery

Since **the severity of anxiety/nervousness before surgery** were ordered-bivariate data, and the pain scores met the criteria of skewed distribution, the analysis of Goodman and Kruskal's Gamma was applied.

HA group

On all four time points, the relationship of **the severity of anxiety/nervousness before surgery** and pain scores demonstrated statistical significant differences in HA group. (**Chart 7**)

a) About the pain scores of initial needling. Gamma=0.417, P<<0.01. Statistical significant differences were noticed, which indicated **the**

severity of anxiety/nervousness before surgery did affect the pain scores of initial needling in HA group.

b) About the pain scores of injection/infusion. Gamma=0.391, P<<0.01.Statistical significant differences were noticed, which indicated **the severity of anxiety/nervousness before surgery** did interfere the pain scores of injection/infusion in HA group.

c) About the pain scores during operations. Gamma=0.289, P=0.003.Statistical significant differences were noticed, which indicated **the severity of anxiety/nervousness before surgery** did affect the pain scores during operations in HA group.

d) About the pain scores after operations. Gamma=0.416, P<<0.01.Statistical significant differences were noticed, which indicated **the severity of anxiety/nervousness before surgery** did affect the pain scores after operations in HA group.

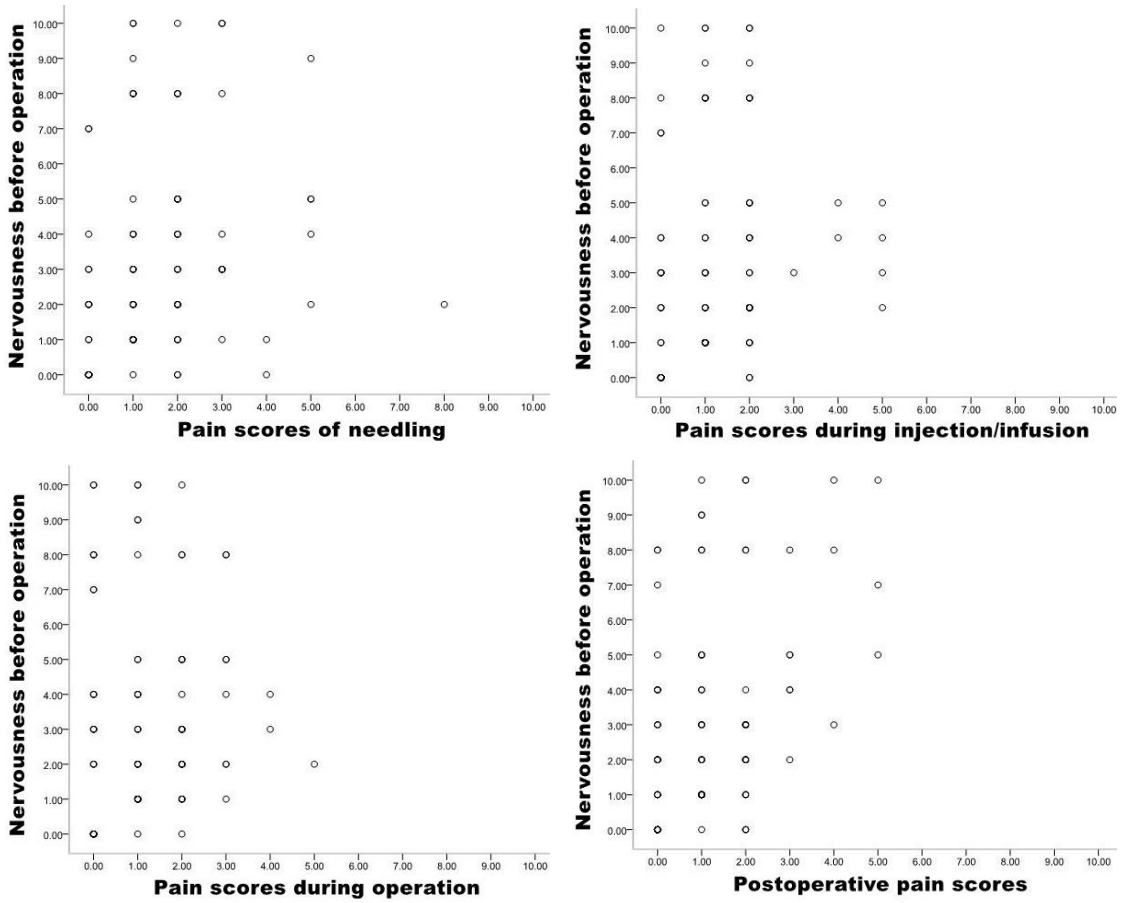

Chart 7. The correlation diagram of the severity of anxiety/nervousness before surgery and pain scores in HA group. The severity of anxiety/nervousness before surgery did affect all four-timing pain scores in HA group (P<0.05)

SIA group

On all four time points, the relationship of **the severity of anxiety/nervousness before surgery** and pain scores demonstrated statistical significant differences in SIA group. (**Chart 8**)

a) About the pain scores of initial needling. Gamma=0.381, P<<0.01.Statistical significant differences were noticed, which indicated **the severity of anxiety/nervousness before surgery** did affect the pain scores of initial needling in SIA group.

b) About the pain scores of injection/infusion. Gamma=0.410, P<<0.01.Statistical significant differences were noticed, which indicated **the severity of**

anxiety/nervousness before surgery did affect the pain scores of injection/infusion in SIA group.

c) About the pain scores during operations. Gamma=0.348, P<<0.01.Statistical significant differences were noticed, which indicated **the severity of anxiety/nervousness before surgery** did affect the pain scores during operations in SIA group.

d) About the pain scores after operations. Gamma=0.348, P<<0.01.Statistical significant differences were noticed, which indicated **the severity of anxiety/nervousness before surgery** did affect the pain scores after operations in SIA group.

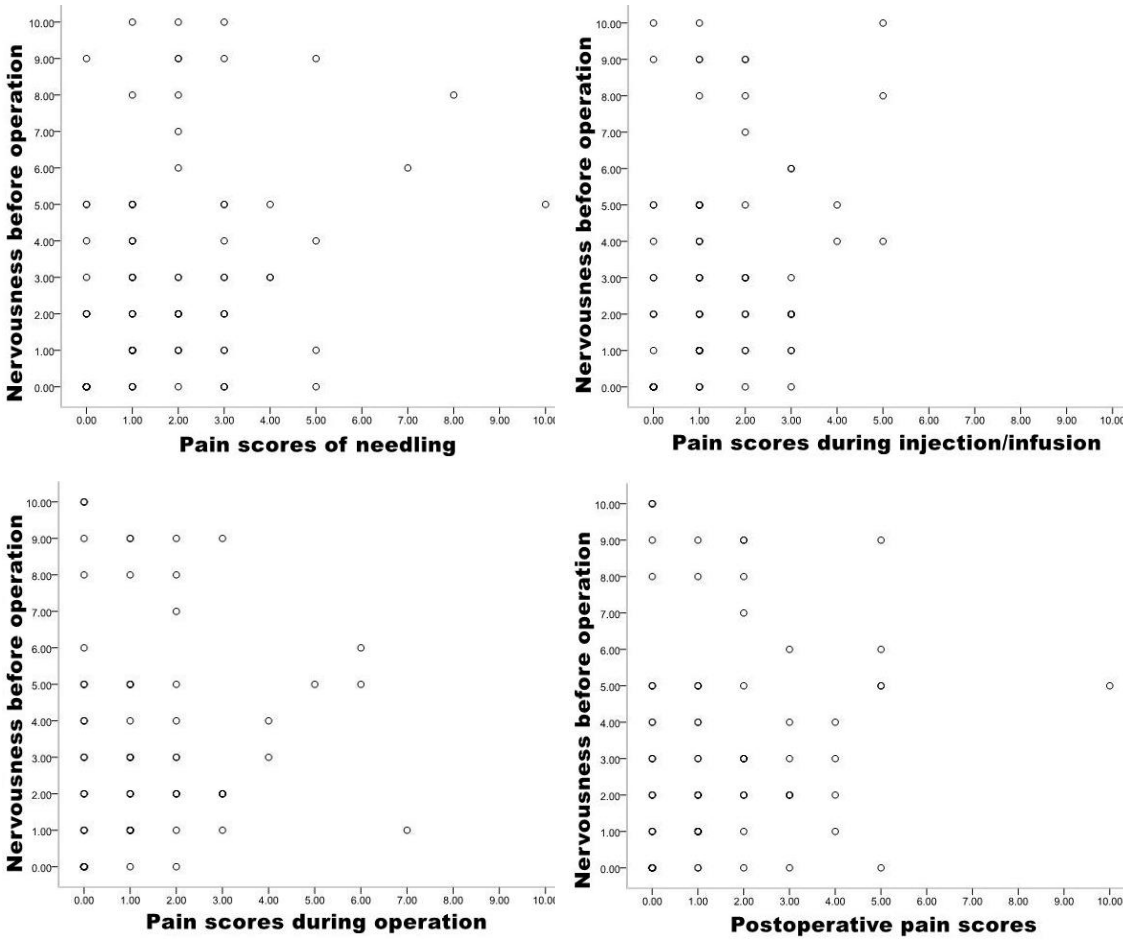

Chart 8. The correlation diagram of the severity of anxiety/nervousness before surgery and pain scores in SIA group. The severity of anxiety/nervousness before surgery did affect all four-timing pain scores in SIA group (P<0.05)

4 Discussion

Local infiltration anesthesia (LIA) is the most common anesthetic technique in dermatological surgery. Compared with general anesthesia, it spares time and labor cost with additional security and convenience. Unfortunately, the pain brought by the process of LIA, which caused by injection and following infusion seems to be unavoidable. As some patients complained after surgery, the pain during the process may overwhelm the expected pain in operation! Therefore, the concerns about how to limit the discomfort of LIA to minimal level, to achieve the best analgesia effect with least complication, have always stayed as a focus in study of LIA.

In this study, we compared randomized two methods of infiltration with a local anesthetic solution. The infiltration by a syringe by hand-actuated anesthesia (HA) and on the other hand a subcutaneous infusion local anesthesia by infusion pumps (SIA). In both groups, the same mixture of local anesthetics was used. This mixture of Lidocaine and Ropivacaine, diluted with an isoionic solution has proven as less painful than commercial solutions. The aim of the study was to find out differences in pain between both infiltration methods. As the study could prove, there was not statistical difference between both methods by low levels of pain (1-2 of 10) , if the infiltration was given slowly (maximum 0.5 ml/sec) with a 30 Gauge syringes.

The reason why SIA and HA had no significant statistical difference in pain management during this study, may lied in several aspects:

1. The high-efficient anesthesia formula. The formula in this study (table 1, in page 4) has proved to be a very efficient one[30] in large amount of patients. The excellent anesthetic effects in both SIA and HA groups might result in the unexpected limited difference in both groups.

2. The slow injection speed and thin Gauge syringes. Due to the improvement of injection equipment and humanistic care, in this study we chose the thinnest needle and low speed. However, this might result in the unexpected limited difference in both groups.

3. The other reasons could be found in the “Limitation of our study” part. (page 50-51)

4.1 The methods for pain relieving in the process of LIA

In fact, in last century, a number of experts have tried sorts of methods to relieve the pain during the LIA process, e.g. skin cooling, vibration, solution warming, choosing proper needle type as well as anesthetic agent, buffering, dilution, topical anesthesia, stroking the skin, and slow infusion tumescent anesthesia. After literature research, we found the results as below:

- **Skin cooling**

  Bechara[19] investigated the pain reduction effect of skin cooling in botulinum toxin A injection for patients with focal axillary hyperhidrosis. Statistically significant lower injection scores were observed both in the air-cooled and ice-cooled sides, compared with noncooled sides. Similar results were found in the study of Goel[20], when they applied ice for 2 minutes under sterile conditions before the local anesthetic injection. However, some other trials[21;22], which focused on the pain reduction of vaccine injection, indicated that pain response did not differ significantly between children received ice compress and who did not.

- **Vibration**

  Li[5] investigated the efficacy and safety of topical vibration anesthesia to reduce pain from botulinum toxin A injections in Chinese patients. Both clinically and statistically significant reduction of pain were observed in the vibration-applied side.

- **Warming anesthetic solution**

  The study of Colaric[6] indicated that warmed lidocaine had no superior pain-reduce effect than plain lidocaine. However, the warmed and buffered lidocaine caused significant less pain than plain lidocaine, warmed lidocaine, or buffered lidocaine. The study recommended the warmed and buffered lidocaine as common clinical practice.

- **Buffering anesthetic solution**

  Adding sodium bicarbonate into the anesthetics is the most common method of

buffering, with an anesthetic-to-buffer ratio of either 9:1 or 10:1[23;24]. Among these studies, many reported less painful mean injection pain scores in groups receiving the buffered agent.

- **Choice of Needle type**

  Yu[25] compared equal-gauge needles and anesthetics (lidocaine, 2%; 27-gauge needle) with either a blunt or a sharp tip in local anesthesia of upper blepharoplasty. The study found statistically significant lower injection pain scores as well as less bruise and hematoma with blunt-tipped needles.

- **Choice of anesthetic agent**

  Steele[26] found articaine at a concentration of 4% caused less pain than 2% lidocaine .Han[27] investigated the pain evaluation of anesthetics with 3 different formulas. Results indicated standalone 2% lidocaine was found to be superior to 2% lidocaine with added epinephrine (1:100,000), and both were superior to a 1:1 mixture of 2% lidocaine with epinephrine (1:100,000) and bupivacaine.

- **Stroking the skin close to the injection site before and during injection**

  Sparks[28] investigated the pain-relieved effect of injection by stroking the skin. The study revealed lower pain scores in children with intervention of stroking than children without.

- **Slow tumescent infusion anesthesia(SIA)**

  Breuninger[7] had found the method of SIA by injecting anesthetic solutions slowly with a common infusomat, as in paravenous infusion, into the subcutaneous layer. Compared with former conventional syringe injection or general anesthesia, patients preferred SIA after the different experience.

- **Mixture of anesthetic agents**

  For purpose of slow tumescent infusion anesthesia, a special mixture of local anesthetic drugs was used in a high dilution. In a bag of 500 ml Inosteril®, which was a isoionic solution, was added with 20 ml of Lidocain 2% and 20 ml 0f Ropivacaine 1%. To this mixture was added 0.5 ml Adrenaline (1:1000.000)

(Table 2). This isoionic diluted mixture has been proven to be less painful during injection given by the infusion pump or by hand with a syringe in contrast to commercially available solutions. But in this investigation the mixture and the commercial solution was not compared.

4.2The advantages of SIA

The SIA method, which has been studied in this 6-month research, has been actually applied in dermatological department of Tuebingen University for decades. Its main physical mechanism is using the infusion pump to inject the anesthetic solution into subcutaneous tissue or even deeper, so as to obtain the intraoperative and postoperative analgesia.

According to our clinical experience, the SIA method has such advantages as below:

a) **Reducing the pain during the process of LIA.** To some extent, the injection method and infusion speed could attribute to the pain of LIA. One of the main factors that would affect the decision, what kind of injection method and infusion speed the surgeon will choose, is the limited time for LIA before operation. For example, the dermatological surgeons of Tuebingen University have about 60 operations to complete each day, which means every surgeon has over 10 operations every single working day. Since the time is so limited for each patient, if using HA, the operator may chose to do multiple injection with fast infusion, which could lead to unendurable pain. Furthermore, by using HA, to achieve immediate analgesia effect, the operator may choose intracutaneous injection, which appears to be much more painful than subcutaneous injection[29]. On the contrary, by using SIA, the multiple patients could be taken care of, by one operator at the same moment during the anesthetic process. So that every single patient has much more precious time for the anesthetic preparation. The operator could adjust the injection points and amounts, the pumping speed, and the volume of anesthetic solution, according to the operative

location, size, the skin tension and the patient's tolerance of pain, which results in individual pain-relieving process with reduced discomfort.

b) **It could offer analgesia for large-area operations.** Conventionally, large-size tumor removing, large-size defect repair, sentinel node biopsy, lymph node dissection and varicose vein surgery need to be operated under general or regional block anesthesia. However, SIA could offer 5*5cm~10*10cm (depended on the location, skin tension and other factors) operative field with analgesia with single injection spot (Fig3.). Meanwhile, to some extent, reducing the injection spots could also bring down the following pain and labor spending. As for the surgery needs multiple injections, due to the coverage of the initial anesthetic zone, the following injections were painless.

c) **It provides high security.** When the pressure rises to a certain level, the infusion pump would stop automatically, so that the excessive pumping could be prevented. In addition, the infusion pump will sound alarm, which would draw the operator back immediately to the patient's side to check his/her condition. Then the ending of anesthesia or the following anesthesia would be decided. Furthermore, in order to prevent the serious toxic complications caused by accidental injection into vessel, all the patients before SIA should be supervised by electrocardiogram monitors. Until today, no clinical case with serious complications caused by SIA was reported, after decade-application in dermatological department of Tuebingen University.

d) **It improves the working efficiency.** The same operator, who could turn to another patient that need analgesia, after he/she places everything in order. That means, one operator could provide anesthetic service to 5-6 patients at the same moment, which tremendously accelerate the process of preparation before surgery.

e) **It relieves the patient's anxiety, and improves the feeling of comfort.** Some patient complains that, the long-time injection by hand, may bring them extra anxiety. To the contrary, the SIA offers them the similar experience as making

"self-service coffee", which makes them more eased before the operation.

4.3 The advantages of anesthetic formula in this study

In this study, the formula of the anesthetic solution in SIA, was created by the surgeons in dermatologic department of Tuebingen University, according to their clinical experience and literatures[30]. In over 30.000 clinical cases, the formula showed well tolerance and brought high-quality analgesia effect. So far it has shown theses advantages as below:

a) **It provides high-quality analgesia effect in large-area operations.** In dermatological surgery, the surgeons have lots of opportunities to confront patients with large-size and deep-thickness tumors. In these cases, whether in removing or fixing stage, a well-tolerance operation should be warranted by good analgesia. However, the formula except for tumescent anesthesia, has the highest doses limitation (as for lidocaine, normally less than 400mg; as for procaine , normally less than 1.5g/h), which can't match the demand for large-area operations. Furthermore, in the conventional formula for tumescent anesthesia(2% lidocaine 20~50ml, epinephrine 1mg, 5%$NaHCO_3$ 5~20ml, NS 1000ml), the main ingredient—lidocaine, has the disadvantage of vasoconstriction[17], which may leads to constant postoperative edema and numbness. To the contrary, the formula of SIA, due to the vasodilator effect of ropivacaine[31], has less complication as mentioned above. The injection with little pain which is proved in this study may be caused by the used anesthetic mixture, a slow injection by hand with 0.5 ml / second as well as the use of a 30 Gauge needle. Therefore the difference of pain in both groups HA and SIA may show no significance.

b) **It contributes to high-quality analgesia for operation.** A handful of literatures show that the formula of SIA benefits in abundant operations, including in digital nerve-block anesthesia and in penile nerve-block anesthesia, as well as in ear and nose surgery[32]. In Tuebingen University, over 30,000 patients underwent various

kinds of surgery, including e.g. basal cell carcinoma, squamous cell carcinoma, lentigomaligna, malignant melanoma, under the SIA at these locations. The formula of SIA provides not only adequate analgesia, but also reduction of bleeding during operation. Therefore, the duration of operation and less electrocautery could be conducted, which lead to raised healing rate.

c) While comparing with the general anesthesia in complete lymph node dissection (CLND), **it provides less complications as well as better cost-effectiveness**[33]**.** Furthermore, it doesn't affect the overall survival and disease-free survival time. There're always controversy that whether the tumescence anesthesia would affect the prognosis due to the potential tumor spread and stimulation in the CLND of patients with melanoma. However, the research of Tuebingen Univerity[34], which involved 281 patients underwent CLND and followed up by 70 months in average, showed that there's no significant difference in overall survival and disease-free survival time between the patients underwent general anesthesia and tumescence anesthesia.

4.4 The influence of six factors on anesthetic effect

According to the clinical results, the factors (age, gender, defect size, the dose of anesthetic, time-period of anesthetic procedure, severity of anxiety/nervousness before surgery) sometimes did affect the final anesthetic effect. Furthermore, the effect in HA and SIA groups was respectively different.

a) **The impact of age on the analgesic effect.** Whether age dose affect the analgesic effect? Some experts have done research on this spot. Adamus[35] have divided the patients scheduled for surgery under total intravenous anesthesia into 4 group, according to the gender and age (20-40 yrs, and 60-75 yrs). The pharmacodynamics of 0.6 mg/kg rocuronium was investigated. Results indicated that, compared with younger patients (both in male and female groups), the elder patients had longer onset time as well as longer anesthetic duration and interval to full spontaneous

recovery. The study implied that intravenous anesthetics may have lower metabolic rate in elders. Some other experts[36] have investigated the anesthetic effect of lidocaine-prilocaine (EMLA) emulsion and music distraction on the pain of intravenous cannulation in different age-related groups. Results demonstrated that EMLA had better anesthetic effect for younger children. Our study had revealed the elder patients suffered more pain during injection in HA group. The result might indicate when using HA methods, low-speed injection is recommended for elder patients, in order to relieve the discomfort during injection.

b) **The impact of gender on the analgesic effect.** Research were been done on the question whether gender do affect the intraoperative and postoperative analgesic effect. Chia[37] investigated the gender as well as other factors influencing morphine requirement for patient-controlled-iv morphine analgesia during the first three postoperative days in 2298 Chinese patients. The results showed that females consumed significantly less morphine than males. Gender was the strongest predictor for postoperative morphine requirements. The research from Periasamy[38] also indicated males consumed significantly higher amount of morphine when compared to females during the first 24 hours after abdominal surgeries. Besides, some review[39] revealed that males and females have much difference in development of CNS, due to the genetic, anatomic as well as the hormonal differences. These sexual differences in anesthetics exist in every each life stage, including children, adult and advanced age. Furthermore, females have lower relative average body weight, higher average body fat, lower average plasma volume, and lower average organ blood flow than males that can influence volume of distribution (VD). The VD. defined as the ratio of the plasma concentration to the amount of drug in the body, is affected by individual body mass index, body composition in relation to water and fat content, plasma volume, organ. Thus the anesthetic difference between males and females occurs in the induction, maintenance and recovery phases. Our study demonstrated that females suffered

more pain during injection in HA group, which might indicate that low-speed injection is relatively more recommended in females when using HA method.

c) **The impact of defect size on the analgesic effect.** Takiguchi[40] evaluated the differences in postoperative physical activity between Laparoscopy-assisted distal gastrectomy (LADG) and open distal gastrectomy (ODG). The Length of longest wound in group LADG is 5.2 (4.9–5.5)cm while in group ODG is 17.0 (16.9–18.1)cm. Significant differences were observed with a more favorable outcome noted in the LADG group with respect to total amount of pain rescue , as well as intraoperative blood, postoperative hospital stay. The postoperative VAS score for pain at rest and walking are significantly lower in LADG group than ODG group. Our study showed, postoperative pain was positively correlated with defect size in HA group. The result might indicate that larger defect size may bring more postoperative pain, when HA method is applied.

d) **The impact of the dose of anesthetic on the analgesic effect.** Some experts[41] had found the main determinant of continuous peripheral nerve block effects, was total drug dose rather than local anesthetic concentration and volume. Their research indicated that in continuous posterior lumbar plexus blocks, patients required the same milligram per hour of ropivacaine in a dilute (0.1%) solution as in a concentrated one (0.4%) and had the same degree of motor block. Another research[42] showed that during induction of anesthesia with propofol, injection over 2 min minimized the induction dose. In contrary, more rapid injection increased dose requirements instead of significant hastening the phase of induction. Our study indicated both in HA and SIA group, the dose of anesthetic had no significant influence on analgesic effect.

e) **The impact of the time-period of anesthetic procedure on the analgesic effect.** Study[42]showed that during induction of anesthesia with propofol, the maximum depth of anesthesia occurred 2-3 min after cessation of injection, shorter procedure might increased dose requirements. However, further investigation about how the

duration of anesthetic procedure affected analgesic effect was missing in literature. Our study demonstrate that, both in HA and SIA group, the pain scores were positively correlated with the duration of anesthetic procedure at all-four time points. We consider this phenomenon might resulted from the anxiety, hyperventilation and other potential factors, which need further investigation.

f) **The impact of the severity of anxiety/nervousness before surgery on the analgesic effect.** Liau[43] investigated the cardiovascular influence of dental anxiety during local anesthesia for tooth extraction. One hundred and eighty patients scheduled to receive routine dental extraction were enrolled. Anxiety was measured at 15 minutes before local anesthetic delivery. Cardiovascular response data including blood pressure, heart rate, O2 saturation, and electrocardiographic changes were measured at 5 time points from 5 minutes before to 15 minutes after the administration of anesthetic. Results showed that high anxiety, younger age, and traumatic dental history were correlated with greater increases in heart rate during the administration of local dental anesthesia. Another research[41] showed that increased cardiac output decreased depth and duration of anesthesia. From the two points above, the possibility which anxiety might result in decreased depth and duration of anesthesia by affecting the cardiac output could be expected. Our study demonstrated, both in HA and SIA group, the postoperative pain score were positively correlated with the anxiety before surgery. The result could be interpreted by the influence of anxiety on cardiac output, which coincide with the literature mentioned above.

4.5 The limitation of SIA itself.

Despite the benefit of SIA as time sparing and high-quality analgesia in lots of dermatologic operations, it has its own limitations.

4.5.1 The possibility of wetting the operation area. Since SIA use the infusion pump as engine, several procedures have the risks for the anesthetic leaking.

a) Before injection. Usually the test before injection, which used to make sure the pump's in normal condition and no bubbles in the tube, is necessary. During the test, the leaking is possible.

b) The switch of needle's location, especially in large-size-defect operation, which may need multiple injections, increases the risk of leaking.

c) The accidental dropping of the needle. Due to the patient's movement or the poor fixation from the adhesive tape, it's possible for the needle to drop from the original location. In this case, besides the leaking, the risk of the accidental needling and the patient's extra nervousness definitely exists. Therefore, the operator must confirm that the fixation of the needle is reliable.

d) At the end of infusion, due to the pressure in the tube, the anesthetic has opportunity to leak when the needle is drawn outside the skin.

4.5.2 The excessive edema. Usually more anesthetic is injected into the target tissues. Therefore, the excessive edema is very common. Normally it vanishes automatically in one day. However, sometimes it could bring higher tension during closing, and the suspended wound healing. In certain areas, e.g. circumocular regions, the edema will last longer and might affect the patient's satisfaction after the surgery for some days but it remains never irreversible.

4.5.3 Adequate supervision of vital sign is necessary. During SIA, the operator lacks the opportunity to make drawing- back test, which used to confirm the needle is not in the vessels. So the monitor for supervising the vital signs of the patient should be immediately and correctly installed before SIA. Due to the adrenaline, the increased heart-beating race would trigger the alarm of the monitor. Thus the operator may realize the urgent situation and solve the problems in time. Therefore, every patient need one monitor and relative facilities and space, which may increase the material cost.

4.5.4 The operator needs certain experience to master SIA. During SIA, test

of drawing back is not available. Besides, the capabilities of choosing the optimal infusion speed, the appropriate anesthetic dose, the location/angle/depth of injection, and settling a stable fixation are necessary for SIA practice. Furthermore, the operator needs to take care of several patients at the same time, as well as to comfort the patients and to eliminate their doubts. All these actions need certain experience, which may require plenty practice at the initial stage.

Despite the limitation of SIA, it is a promising anesthetic method with high efficiency and ideal quality.

4.6 The limitation of our study included:

a) The grouping of our patients was not double-blind designed. Due to the limited research labor, the operator (doctoral candidate Mingyi Chen) who did the local anesthesia was also the same person who delivered and collected the questionnaires. But this may be an advantage on the other hand, because the doctoral candidate was not interested in one of the methods (seen chapter c).
b) The study lacked very exact time point, which could be used to evaluate the anesthetic onset efficiency.
c) Since the same operator (Doctoral candidate Mingyi Chen) collected the pain-evaluating questionnaire, the potential bias could happen. However, because the investigator was not part of the surgical team, he had a mental indifference concerning the methods. Furthermore, if two or more operators were involved, they might have different approaches for inserting the needles or injecting the fluid.
d) The main pain-evaluating score were relatively subjective, which exacted from the patients' memory about the injection and operation. More objective scores may improve the stringency of the study.
e) The estimation of sample size. At the very beginning, due to the confidence of

the positive results and clinical experience, the sample size was not estimated. However, according to the subsequent evaluation results of sample size (in page 9, line 1-20), the sample size we adopted was sufficient. Even so, the same fault should always be noticed in the further study.

f) The bias from VAS scores derived partly by patients and partly by investigator. Because some well-understanding patients chose to directly give the scores by themselves, the investigator found it had no reason and impolite to ask them to mark the crossings again on questionnaires. Thus would result in mild bias because of different standards., even the patients directly gave scores made up only very small proportion. Actually, letting all patients drew crossing maybe better choice. In the further study, this fault should be noticed.

g) The absence of Consort Flow Diagram. Even all 200 patients received the allocated intervention and completed the follow-up. However, the absence of Consort Flow Diagram missed the patients who declined to take part in this study, or who didn't meet the inclusion criteria. In the further study, this fault should be noticed.

h) Theoretically, the institution of data and statistical analysis would be better to be the department of Clinical Epidemiology and Applied Biometric in Tuebingen. However, the candidate needed to return to China after his investigation. In order to complete the study, he had to ask for the advice of a statistical expert in China. Following the premise of data anonymity and protection, only the anonymous and randomly generated data was provided to acquire the statistical advice. Even so, the potential risk of unconsistency to informed consent still mildly exited. In the further study, the investigation and data analysis would better both been done in University Tuebingen.

5 Summary

Local infiltration anesthesia (LIA) plays a key role in routine dermatological surgery. The smooth process of surgery and the high satisfaction from patient depend on greatly on the qualified and pain-relieved LIA.

In our study, by using a painless mixture of Lidocaine and Ropivacaine highly diluted with an isoionic solution, the comparison of slowly performed (0.5 ml / second) hand-actuated local anesthesia (HA) and subcutaneous infusion local anesthesia (SIA) was performed. We found very low pain scores, but in contrast to our expectations, no statistical significant difference of pain scores at the needling, injection/infusion, during and after operations. This means HA can be applied with low pain. This study is limited to these both infiltration methods and the use of the special solution of local anesthetics. However, comparison to other local anesthetic drugs is not possible in this study.

By using SIA, one person could offer anesthesia to several patients at the same time. Furthermore, many patients preferred this kind of semi-automatic anesthesia. SIA is able to develop as an effective anesthetic method. The limitations of SIA consisted of requirement for constant supervision and the experience of operators' experience, which still need further improvements and standardizations in the future. We believe SIA is a promising local anesthesia method in dermatological surgery with a broad application area.

In another aspect, the impact of 6 factors (age, gender, defect size, dose of anesthetic solution, duration of the procedure, the severity of anxiety/nervousness) on the analgesia effect in both HA and SIA group were investigated. Results showed age, gender and defect size did have certain influence on the analgesia effect in HA group. Particularly duration of the procedure and the severity of

anxiety/nervousness had significant impact on the analgesia effect in both two groups at all four timings. The results proved the importance of shortening the anesthetic procedure and relieving the anxiety before surgery.

Zusammenfassung

Die lokale Infiltrationsanästhesie spielt eine Schlüsselrolle in der Dermatochirurgie. Die angenehme Durchführung mit hoher Patientenzufriedenheit hängt stark von eine qualifizierten und schmerzarmen Infiltration ab.

Unsere Studie die eine hoch verdünnte Mischung von Lidokain und Ropivakain in einer isoionischen Lösung benutzte, verglich langsam injizierte (0,5 ml / Sekunde) Lokalanästhesie von Hand (HA) mit subkutaner lokaler Infusionsanästhesie (SIA). Wir fanden sehr niedrige Schmerz-Scores, jedoch keinen statistischen Unterschied in den Schmerz-Scores während der Injektion/Infusion und während der Operation. Das bedeutet, dass auch die Handinjektion mit geringem Schmerz verabreicht werden kann wenn die beschriebene lokalanästhesielösung verwendet wird . Aber diese Studie ist auf die beiden genannten Injektionsformen begrenzt. Ein Vergleich mit anderen Lokalanästhesie-Lösungen ist nicht möglich. Bei der Anwendung der SIA kann jedoch eine Person bei mehreren Patienten gleichzeitig eine lokale Infiltration durchführen. Darüberhinaus bevorzugen viele Patienten diese Art der semiautomatischen Injektion. SIA könnte sich hier weiter als effiziente Methode entwickeln. Die Begrenzung von SIA, die Notwendigkeit einer konstanten Supervision und die Erfahrung der ausführenden Personen bedürfen noch der Verbesserung und Standardisierung. Wir glauben, dass SIA eine erfolgversprechende Methode für die Dermatochirurgie darstellt mit breitem Anwendungsbereich.

Unter weiteren Aspekten wurde in der Studie die Bedeutung von 6 Faktoren (Alter

des Patienten, Geschlecht, Defektgröße, Dosis der Anästhesie-Lösung, Dauer der Prozedur und der Grad der Ängstlichkeit/Nervosität) auf den analgesiereden Effekt in beiden Gruppen (HA und SIA) gemessen. Die Ergebnisse zeigen, dass das Alter, Geschlecht und die Defektgröße einen gewissen Einfluss auf den analgesierenden Effekt in der HA Gruppe hatten. Insbesondere hatten die Dauer der Prozedur und eine starke Ängstlichkeit/Nervosität einen signifikanten Einfluss auf den Analgesie-Effekt in beiden Gruppen bei allen Intervallen der Messungen. Die Ergebnisse zeigen die Wichtigkeit der die Prozedur der Lokalanästhesie kurz zu halten um die Ängstlichkeit und Nervosität zu vermindern.

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7 Declaration of contributions

This study was performed in the dermatological department of Eberhard Karls University of Tübingen, under the supervision of Pro. Dr. Helmut Breuninger.

Doctoral candidate Mingyi Chen carried out all the local anesthesia, clinical investigations and data collection. He contributed to the delivery and collection of questionnaires. He was also involved in the design of this study, and wrote the manuscript independently.

Pro. Dr. Breuninger contributed to the study design, supervised the work, and corrected the manuscript. He also contributed to the design and improvement of questionnaire, the application of ethical committee' permission, as well as the translation of this dissertation's summary into German.

With the permission of Prof. Dr. Hans-Martin Häfner, doctoral candidate Mingyi Chen had the opportunity to carry out the study in dermatologic department of Tübingen University. Furthermore, he taught Mingyi Chen surgical techniques and the skills of communication with patients.

Dr. Saskia Schnabl contributed to the design and the improvement of the questionnaire.

Dr. Franziska Ghoreshi helped Mingyi Chen of being acquainted with the procedures and instructions of dermatologic surgeries, at the initial time of clinical operation in Tübingen.

Mr. Jin-liang Hu (from China) contributed to the statistical analysis.
The institution of Department of Clinical Epidemiology and Applied Biometry of

Tuebingen University contributed to the randomization with the computer-generated random numbers.

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